МОЛЕКУЛЯРНАЯ БИОЛОГИЯ, 2023, том 57, № 4, с. 665–667

МОЛЕКУЛЯРНАЯ БИОЛОГИЯ КЛЕТКИ

УДК 575.113.5:575.117.2

JMJD3 ПРОЯВЛЯЕТ ОНКОРЕПРЕССОРНУЮ АКТИВНОСТЬ В КЛЕТКАХ ОСТРОГО ПРОМИЕЛОЦИТАРНОГО ЛЕЙКОЗА, СТИМУЛИРУЯ ЭКСПРЕССИЮ PU.1[1]

© 2023 г. M.-X. Wang[a, b], S.-H. Yu[a], M. Xiao[c, *], J. Chen[a, **]

[a]*Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine at Shanghai, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200025 China*

[b]*Department of Medical Oncology, Xuzhou Central Hospital, Xuzhou Medical University, Xuzhou, 221009 China*

[c]*Shanghai Ji Ai Genetics and IVF Institute, the Obstetrics and Gynecology Hospital of Fudan University, Shanghai, 200011 China*

**e-mail: xiaomin3296@163.com*

***e-mail: chenjuanrj@163.com*

Поступила в редакцию 27.08.2022 г.
После доработки 02.11.2022 г.
Принята к публикации 03.11.2022 г.

Полностью *транс*-ретиноевая кислота, применяемая в терапии острого промиелоцитарного лейкоза, известна как часто используемый для индукции дифференцировки препарат, который восстанавливает экспрессию ключевого фактора транскрипции PU.1, детерминирующего нормальный гемопоэз клеток миелоидной линии. Ранее мы обнаружили, что индуцируемая стрессом гистондеметилаза H3K27 – JMJD3 – прямо активирует экспрессию PU.1, что стимулирует коммитирование миелоидных клеток в ходе нормального миелопоэза. Кроме того, JMJD3 действует как онкорепрессор и играет критически важную регуляторную роль в инициации и прогрессии злокачественного гемопоэза. В настоящей работе продолжено изучение связи между JMJD3 и PU.1 при остром промиелоцитарном лейкозе, при котором JMJD3 проявляет онкосупрессорную активность, стимулируя экспрессию PU.1.

Ключевые слова: острый миелоидный лейкоз, гистондеметилаза, JMJD3, PU.1, миелоидная дифференцировка

DOI: 10.31857/S0026898423040213, **EDN:** QMAEUQ

СПИСОК ЛИТЕРАТУРЫ

1. Geissmann F., Manz M.G., Jung S., Sieweke M.H., Merad M., Ley K. (2010) Development of monocytes, macrophages, and dendritic cells. *Science*. **327**(5966), 656–661.
2. Lieschke G.J., Oates A.C., Paw B.H., Thompson M.A., Hall N.E., Ward A.C., Ho R.K., Zon L.I., Layton J.E. (2002) Zebrafish SPI-1 (PU.1) marks a site of myeloid development independent of primitive erythropoiesis: implications for axial patterning. *Dev. Biol*. **246**(2), 274–295.
3. Scott E.W., Simon M.C., Anastasi J., Singh H. (1994) Requirement of transcription factor PU.1 in the development of multiple hematopoietic lineages. *Science*. **265**(5178), 1573–1577.
4. DeKoter R.P., Singh H. (2000) Regulation of B lymphocyte and macrophage development by graded expression of PU.1. *Science*. **288**(5470), 1439–1441.
5. Dahl R., Walsh J.C., Lancki D., Laslo P., Iyer S.R., Singh H., Simon M.C. (2003) Regulation of macrophage and neutrophil cell fates by the PU.1:C/EBPalpha ratio and granulocyte colony-stimulating factor. *Nat. Immunol.* **4**(10), 1029–1036.
6. Fisher R.C., Scott E.W. (1998) Role of PU.1 in hematopoiesis. *Stem Cells*. **16**(1), 25–37.
7. Pham T.H., Benner C., Lichtinger M., Schwarzfischer L., Hu Y., Andreesen R., Chen W., Rehli M. (2012) Dynamic epigenetic enhancer signatures reveal key transcription factors associated with monocytic differentiation states. *Blood*. **119**(24), e161–e71.
8. Herault A., Binnewies M., Leong S., Calero-Nieto F.J., Zhang S.Y., Kang Y.A., Wang X., Pietras E.M., Chu S.H., Barry-Holson K., Armstrong S., Gottgens B., Passegue E. (2017) Myeloid progenitor cluster formation drives emergency and leukaemic myelopoiesis. *Nature*. **544**(7648), 53–58.

[1] Статья представлена авторами на английском языке.

9. Paz-Priel I., Friedman A. (2011) C/EBPalpha dysregulation in AML and ALL. *Crit. Rev. Oncog.* **16**(1–2), 93–102.
10. Anguita E., Gupta R., Olariu V., Valk P.J., Peterson C., Delwel R., Enver T. (2016) A somatic mutation of GFI1B identified in leukemia alters cell fate via a SPI1 (PU.1) centered genetic regulatory network. *Dev. Biol.* **411**(2), 277–286.
11. Van Thillo Q., De Bie J., Seneviratne J.A., Demeyer S., Omari S., Balachandran A., Zhai V., Tam W.L., Sweron B., Geerdens E., Gielen O., Provost S., Segers H., Boeckx N., Marshall G.M., Cheung B.B., Isobe K., Kato I., Takita J., Amos T.G., Deveson I.W., McCalmont H., Lock R.B., Oxley E.P., Garwood M.M., Dickins R.A., Uyttebroeck A., Carter D.R., Cools J., de Bock C.E. (2021) Oncogenic cooperation between TCF7-SPI1 and NRAS(G12D) requires beta-catenin activity to drive T-cell acute lymphoblastic leukemia. *Nat. Commun.* **12**(1), 4164.
12. Swigut T., Wysocka J. (2007) H3K27 demethylases, at long last. *Cell.* **131**(1), 29–32.
13. Salminen A., Kaarniranta K., Hiltunen M., Kauppinen A. (2014) Histone demethylase Jumonji D3 (JMJD3/KDM6B) at the nexus of epigenetic regulation of inflammation and the aging process. *J. Mol. Med.* (Berl.). **92**(10), 1035–1043.
14. Miller S.A., Mohn S.E., Weinmann A.S. (2010) Jmjd3 and UTX play a demethylase-independent role in chromatin remodeling to regulate T-box family member-dependent gene expression. *Mol. Cell.* **40**(4), 594–605.
15. Shi X., Zhang Z., Zhan X., Cao M., Satoh T., Akira S., Shpargel K., Magnuson T., Li Q., Wang R., Wang C., Ge K., Wu J. (2014) An epigenetic switch induced by Shh signalling regulates gene activation during development and medulloblastoma growth. *Nat. Commun.* **5**, 5425.
16. Chen S., Ma J., Wu F., Xiong L.J., Ma H., Xu W., Lv R., Li X., Villen J., Gygi S.P., Liu X.S., Shi Y. (2012) The histone H3 Lys 27 demethylase JMJD3 regulates gene expression by impacting transcriptional elongation. *Genes Dev.* **26**(12), 1364–1375.
17. Yu S.H., Zhu K.Y., Zhang F., Wang J., Yuan H., Chen Y., Jin Y., Dong M., Wang L., Jia X.E., Gao L., Dong Z.W., Ren C.G., Chen L.T., Huang Q.H., Deng M., Zon L.I., Zhou Y., Zhu J., Xu P.F., Liu T.X. (2018) The histone demethylase Jmjd3 regulates zebrafish myeloid development by promoting spi1 expression. *Biochim. Biophys. Acta Gene Regul. Mech* (1861) (2), 106–116.
18. Yu S.H., Zhu K.Y., Chen J., Liu X.Z., Xu P.F., Zhang W., Yan L., Guo H.Z., Zhu J. (2018) JMJD3 facilitates C/EBPbeta-centered transcriptional program to exert oncorepressor activity in AML. *Nat. Commun.* **9**(1), 3369.
19. Kamens J. (2015) The Addgene repository: an international nonprofit plasmid and data resource. *Nucl. Acids Res.* **43**(Database issue), D1152–D1157.
20. Irizarry R.A., Bolstad B.M., Collin F., Cope L.M., Hobbs B., Speed T.P. (2003) Summaries of Affymetrix GeneChip probe level data. *Nucl. Acids Res.* **31**(4), e15.
21. Gutierrez N.C., Lopez-Perez R., Hernandez J.M., Isidro I., Gonzalez B., Delgado M., Ferminan E., Garcia J.L., Vazquez L., Gonzalez M., San Miguel J.F. (2005) Gene expression profile reveals deregulation of genes with relevant functions in the different subclasses of acute myeloid leukemia. *Leukemia.* **19**(3), 402–409.
22. Ley T.J., Mardis E.R., Ding L., Fulton B., McLellan M.D., Chen K., Dooling D., Dunford-Shore B.H., McGrath S., Hickenbotham M., Cook L., Abbott R., Larson D.E., Koboldt D.C., Pohl C., Smith S., Hawkins A., Abbott S., Locke D., Hillier L.W., Miner T., Fulton L., Magrini V., Wylie T., Glasscock J., Conyers J., Sander N., Shi X., Osborne J.R., Minx P., Gordon D., Chinwalla A., Zhao Y., Ries R.E., Payton J.E., Westervelt P., Tomasson M.H., Watson M., Baty J., Ivanovich J., Heath S., Shannon W.D., Nagarajan R., Walter M.J., Link D.C., Graubert T.A., DiPersio J.F., Wilson R.K. (2008) DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome. *Nature.* **456**(7218), 66–72.
23. Valk P.J., Verhaak R.G., Beijen M.A., Erpelinck C.A., Barjesteh van Waalwijk van Doorn-Khosrovani S., Boer J.M., Beverloo H.B., Moorhouse M.J., van der Spek P.J., Lowenberg B., Delwel R. (2004) Prognostically useful gene-expression profiles in acute myeloid leukemia. *N. Engl. J. Med.* **350**(16), 1617–1628.
24. Haferlach T., Kohlmann A., Wieczorek L., Basso G., Kronnie G.T., Bene M.C., De Vos J., Hernandez J.M., Hofmann W.K., Mills K.I., Gilkes A., Chiaretti S., Shurtleff S.A., Kipps T.J., Rassenti L.Z., Yeoh A.E., Papenhausen P.R., Liu W.M., Williams P.M., Foa R. (2010) Clinical utility of microarray-based gene expression profiling in the diagnosis and subclassification of leukemia: report from the International Microarray Innovations in Leukemia study group. *J. Clin. Oncol.* **28**(15), 2529–2537.
25. Burg J.M., Link J.E., Morgan B.S., Heller F.J., Hargrove A.E., McCafferty D.G. (2015) KDM1 class flavin-dependent protein lysine demethylases. *Biopolymers.* **104**(4), 213–246.
26. Wang Z., Qin G., Zhao T.C. (2014) HDAC4: mechanism of regulation and biological functions. *Epigenomics.* **6**(1), 139–150.
27. Xhabija B., Kidder B.L. (2019) KDM5B is a master regulator of the H3K4-methylome in stem cells, development and cancer. *Semin. Cancer Biol.* **57**, 79–85.
28. Tellier M. (2021) Structure, activity, and function of SETMAR protein lysine methyltransferase. *Life* (Basel). **11**(12). 1342.
29. Kramer O.H. (2009) HDAC2: a critical factor in health and disease. *Trends Pharmacol Sci.* **30**(12), 647–655.
30. Mueller B.U., Pabst T., Fos J., Petkovic V., Fey M.F., Asou N., Buergi U., Tenen D.G. (2006) ATRA resolves the differentiation block in t(15;17) acute myeloid leukemia by restoring PU.1 expression. *Blood.* **107**(8), 3330–3338.
31. Fu W., Zhu G., Xu L., Liu J., Han X., Wang J., Wang X., Hou J., Zhao H., Zhong H. (2022) G-CSF upregulates the expression of aquaporin-9 through CEBPB to enhance the cytotoxic activity of arsenic trioxide to acute myeloid leukemia cells. *Cancer Cell Int.* **22**(1), 195.
32. Duprez E., Wagner K., Koch H., Tenen D.G. (2003) C/EBPbeta: a major PML-RARA-responsive gene in retinoic acid-induced differentiation of APL cells. *EMBO J.* **22**(21), 5806–5816.

JMJD3 Exerts Oncorepressor Activity in Acute Promyelocytic Leukemia by Promoting PU.1 Expression

M.-X. Wang[1, 2], S.-H. Yu[1], M. Xiao[3, *], and J. Chen[1, **]

[1]*Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine at Shanghai, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200025 China*

[2]*Department of Medical Oncology, Xuzhou Central Hospital, Xuzhou Medical University, Xuzhou, 221009 China*

[3]*Shanghai Ji Ai Genetics and IVF Institute, the Obstetrics and Gynecology Hospital of Fudan University, Shanghai, 200011 China*

**e-mail: xiaomin3296@163.com*

***e-mail: chenjuanrj@163.com*

All-trans retinoic acid (ATRA) in acute promyelocytic leukemia (APL) has been the most famous differentiation induction therapy during which the expression of PU.1, a key transcription factor (TF) for myeloid lineage determination in normal hematopoiesis is restored. In our previous studies, we found a stress-inducible H3K27 demethylase, JMJD3, to directly upregulate PU.1 expression to promote myeloid commitment during normal myelopoiesis. In addition, JMJD3 acts as an oncorepressor and plays a critical regulatory role in the initiation and progression of malignant hematopoiesis. In this study, we further resolved the relationship between JMJD3 and PU.1 in APL therein JMJD3 exerts oncorepressor activity via promoting PU.1 expression.

Keywords: acute myeloid leukemia, histone demethylase, JMJD3, PU.1, myeloid differentiation